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Synthesis of the C17-C27 Fragment of Bryostatin 3

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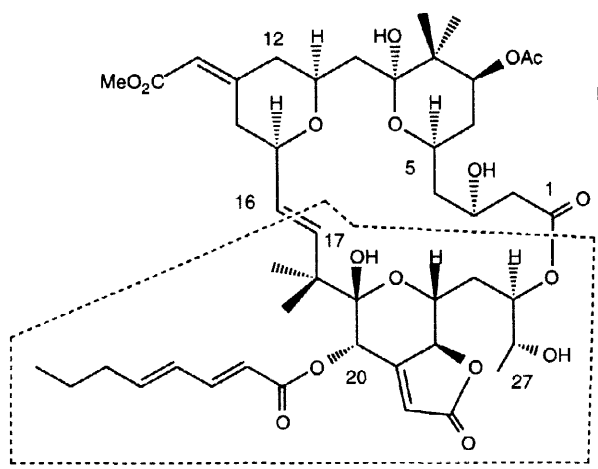
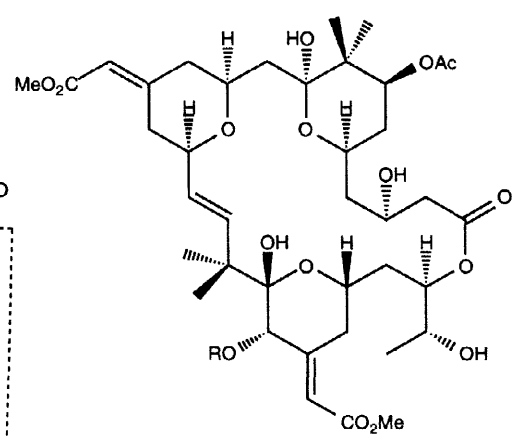
Abstract: The key synthetic intermediate corresponding to the C17 - C27 positions of bryostatin 3, has successfully been synthesized. The newly constructed stereogenic centers were unambiguously confirmed by X-ray crystallographic analysis.

Keywords: biologically active compounds; macrolides; marine metabolites; polyketides

Bryostatins isolated from the marine bryozoan *Bugula neritina* Linnaeus and *Amathia convoluta*, have met expectations as leads for new potent antineoplastic agents.[1] Actually, bryostatin 1 which is the most abundant congener (2.4 x10^{-5}%) in the family, is known to be in Phase II of clinical trials. Additionally, several biologically potential features such as the strong interaction with PKC and the antagonism to phorbol ester have been observed, although the mode of action of this natural product is still under investigation. In addition to such interesting biological properties, insufficient amounts of the natural product, have motivated synthetic studies to obtain samples for further evaluations.[2] Against this background, we have carried out extensive synthetic study on bryostatins.[3] We describe herein synthesis of the bottom half of bryostatin 3,[4] which is a unique member of the family, for the additional γ-lactone moiety.[1a,5]



Bryostatin 3



Bryostatin 1: R= $CO(CH)_4C_3H_7$

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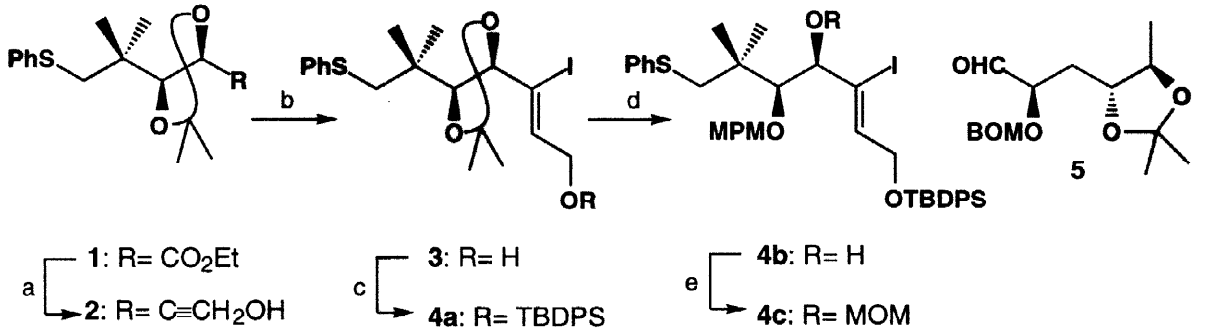
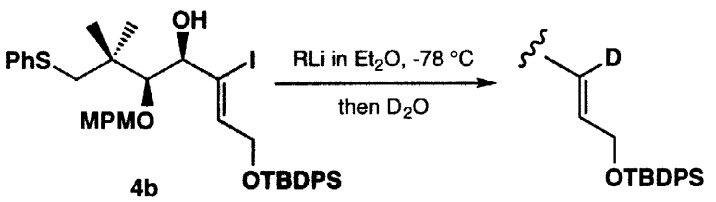


Scheme 1. *reagents*: a. i) DIBAL-H / PhMe, -78 °C; ii) Ph_3P-CBr_4 / CH_2Cl_2, 0 °C (88% in 2steps); iii) n-BuLi / THF, then $(CH_2O)_n$ (87%). b. Red-Al / THF, then I_2 (86%). c. TBDPSCl, Imd (95%). d. i) TFA-H_2O / THF; ii) TBDPSCl, Imd; iii) $MeOC_6H_4CH(OMe)_2$, PPTS / CH_2Cl_2 (77% in 3 steps); iv) DIBAL-H / PhMe, 0 °C (79%). e. MOMCl, i-Pr_2NEt / CH_2Cl_2 (84%).

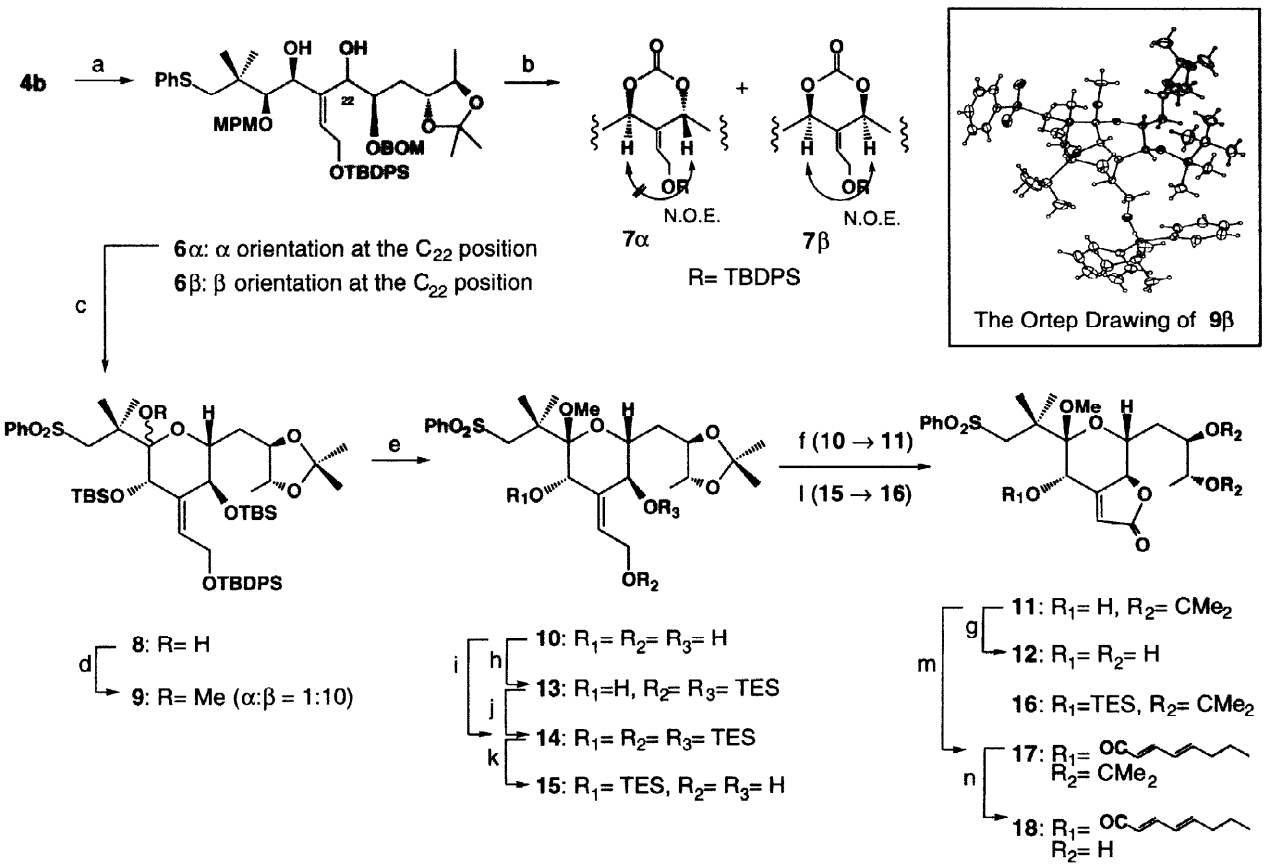


RLi (eq. mol)	Yield % (D %)
n-BuLi (2.5)	40 (0)
t-BuLi (3.5)	90 (10)
t-BuLi (6.0)	77 (30)
MeLi (1.0), then t-BuLi (2.0)	70 (100)
NaH (1.2)	-

Table 1. Generation of the Vinyl Anions of 4b.

The synthesis was commenced with reduction of the known ester **1**,[3c] followed by usual manipulation to give the corresponding propargyl alcohol **2** in good overall yield. Upon hydroalumination and concomitant iodination, **2** was transformed into vinyl iodide **3** (86%), derivatization of which afforded **4a** - **4c**, as shown in Scheme 1. Coupling of these vinyl iodides with aldehyde **5**[6] under $CrCl_2$ - $NiCl_2$, was unsuccessful, probably owing to low reactivities. Accordingly, our attention was turned to a halogen - metal exchange procedure to generate the corresponding vinyl anions, which would facilitate the desired coupling with **5**. The MeLi - t-BuLi conditions were proved to be the method of choice from the extensive assessment of deuterium introduction, as can be seen in Table 1. Actually, successive treatment of **4b** with the corresponding bases, followed by the addition of aldehyde **5** provided a 3:1 mixture of the 1,3-diols (**6**α and **6**β) in 53% yield, whereas the halogen - metal exchange of **4a** and **4c** provided considerable amounts of undesired by-products such as arene derivatives. The stereochemistry of both isomers (**6**α and **6**β) was determined by the N.O.E. experiments of the corresponding cyclic carbonate derivatives **7**α and **7**β.

The major isomer **6**α was converted in five steps into lactol **8**, which on acetalization afforded **9** in 91% yield (α:β = 1:10). The stereochemistry of this compound could be unambiguously confirmed by a single X-ray crystallographic analysis of the major isomer.[7,8] Exhaustive deprotection of the siloxy groups provided the corresponding triol **10**. Reactivity difference among the three hydroxyl groups in **10** allowed the following reactions. Thus, selective oxidation with TPAP effected the one-pot construction of the γ-lactone structure, leading to **11**, the acetonide group of which could be removed under several acid-hydrolytic conditions, to the triol **12** involving a hydroxyl group at the C_{25} position required for macrolactonization. On the other hand, exposure of **10** to TESCl - Imd. afforded the disiloxy ether **13** in 94% yield, while exhaustive etherification under TESOTf - 2,6-lutidine conditions produced **14** (83%), which could also be obtained from **13** under the



Scheme 2. *reagents*: a. MeLi / Et_2O, -30 °C, t-BuLi, -90 °C, then **5** (53%). b. triphosgene, pyr. / CH_2Cl_2, -45 °C (71%). c. i) TBSOTf, 2,6-litidine (99%); ii) m-CPBA, Na_2HPO_4 (99%); iii) DDQ / 10% aq.CH_2Cl_2 (99%); iv) Dess - Martin reagent (99%); v) H_2, $Pd(OH)_2$-C / EtOH, then $Me_2C(OMe)_2$, PPTS / acetone (89%). d. TBSOTf, TMSOMe, $Me_2C(OMe)_2$, MS4Å /CH_2Cl_2 (91%). e. TBAF / THF (quant). f. TPAP, NMO, MS4Å /CH_2Cl_2 (86%). g. CSA / MeOH, or PPTS / MeOH, 60 °C, or Amberlyst 15E / MeOH. 50 °C, or 60% aq.AcOH. h. TESCl, Imd. (94%). i. TESOTf, 2,6-lutidine (83%). j. TESOTf, 2,6-lutidine (86%). k. TBAF - AcOH (1:1) (quant). l. TPAP (100%), or MnO_2 / CH_2Cl_2 (90%). m. (2*E*,4*E*)-octa-2,4-dienoic acid, EDCI, DMAP / CH_2Cl_2 (76%). n. CSA / MeOH (60%).

same TESOTf conditions. Selective removal of the silyl protective group in **14** was effected under TBAF - AcOH conditions to give diol **15** in quantitative yield, which on TPAP or MnO_2 oxidation provided lactone **16** in high yields. Additionally, introduction of the characteristic acyl group at the C_{20} position could be demonstrated by acylation of **11** with (2*E*,4*E*)-octa-2,4-dienoic acid under the EDCI-DMAP conditions, leading to **17**[9] in good yield, which on acid hydrolysis afforded the corresponding diol **18**.[9]

In conclusion, the bottom half fragment (C_{17} - C_{27}) of bryostatin 3 has been successfully synthesized through the halogen-metal exchange reaction. Manipulation of reactivities of the corresponding hydroxyl groups could demonstrate the selective construction of the γ-lacton ring, as well as the feasibility of the acylation at the C_{20} position.

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4. Parts of this study were presented at the Annual Meeting of the Chemical Society Japan (1997, 4G4 17; 1998, 4E7 02).
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6. Essentially the same synthetic method as that for this compound has been published in ref. 3b.
7. Crystal data: $C_{53}H_{84}O_9SSi_3$ (FW=981.56), monoclinic, $P2_1$, a=8.779 (3), b=26.794 (5), c=12.682 (3) Å, β=92.29 (2)°,V=2980.7 (14) $Å^3$, Z=2, Dx=1.094 Mg m^{-3}, T=297 K. X-ray intensities were measured on a Rigaku AFC-5 diffractometer with Mo Kα radiation (λ= 0.71073 Å), and final R=0.060 for 3961 observed reflections. The details have been deposited at the Cambridge Crystallographic Data Center.
8. **9b**: mp 110 - 111 °C (EtOH); $[\alpha]_D^{22}$ +20.6° (*c* 1.00, $CHCl_3$); IR (film) 1588 cm^{-1}; δ_H ($CDCl_3$) -0.04 (3H, s), 0.03 (3H, s), 0.08 (6H, s), 0.82 (6H, s), 0.88 (9H, s), 1.14 (3H, d, J= 3.6 Hz), 1.18 (9H, s), 1.29 (3H, s), 1.34 (3H, s), 1.65 - 1.72 (2H, complex), 1.81 (3H, s), 1.86 (3H, s), 3.40 (1H, m), 3.41 (3H, s), 3.53 (1H, m), 3.82 (1H, br t, J= 9.6 Hz), 3.91 (1H, d, J= 14.8 Hz), 3.98 (1H, d, J= 14.8 Hz), 4.02 (1H, br d, J= 7.2 Hz), 4.15 (1H, br t, J= 8.4 Hz), 4.51 - 4.55 (2H, complex), 4.92 (1H, br s), 6.25 (1H, m), 6.91 - 6.94 (3H, complex), 7.23 - 7.32 (6H, complex), 7.81 - 7.85 (4H, complex); δ_C ($CDCl_3$) -5.1, -4.6, -3.9, -3.7, 17.0, 18.5, 19.4, 23.0, 25.9, 26.3, 27.0, 27.4, 37.0, 46.8, 50.8, 61.0, 64.2, 71.4, 72.2, 75.7, 77.4, 77.6, 78.6, 103.4, 108.1, 127.9, 128.1, 128.3, 128.5, 128.6, 129.0, 130.1, 130.2, 132.6, 136.0, 138.9, 144.0.
9. **17**: $[\alpha]_D^{20}$ -30.8° (*c* 1.00, $CHCl_3$); IR (film): 1795, 1760, 1735, 1650 cm^{-1}; δ_H ($CDCl_3$) 0.95 (3H, t, J= 7.4 Hz), 1.29 (3H, s), 1.30 (3H, s), 1.34 (3H, s), 1.35 (3H, s), 1.46 (3H, s), 1.50 (2H, ddd, J= 15.8, 7.4, 7.2 Hz), 1.94 (1H, ddd, J= 13.8, 10.8, 2.4 Hz), 2.05 (1H, ddd, J= 13.6, 10.4, 2.4 Hz), 2.19 (2H, dd, J= 14, 6.8 Hz), 3.38 (1H, d, J= 14.4 Hz), 3.40 (3H, s), 3.64 (1H, dt, 10, 1.6 Hz), 3.65 (1H, d, J= 14.4 Hz), 3.73 (1H, ddd, J= 16.6, 6, 2.2 Hz), 3.82 (1H, ddd, J= 10, 8, 2.4 Hz), 4.59 (1H, dd, J= 9.2, 2 Hz), 5.68 (1H, d, J= 15.8 HZ), 5.84 (1H, s), 6.08 (1H, d, J= 1.6 Hz), 6.18 (1H, dd, J= 15.6, 10 Hz), 6.25 (1H, dt, J= 15.6, 6.4 Hz), 7.31 (1H, dt, J= 7.6, 1.2 Hz), 7.54 (2H, t, J= 7.6 Hz), 7.64 (1H, dt, J= 7.6, 1.2 Hz), 7.89 (2H, dt, J= 7.6, 1.2 Hz); δ_C ($CDCl_3$) 13.7, 17.0, 21.8, 22.5, 24.0, 27.1, 35.1, 35.4, 45.2, 53.5, 62.8, 68.7, 74.8, 77.2, 78.1, 103.1, 108.1, 116.7, 117.3, 127.5, 128.0, 129.2, 133.4, 142.2, 147.5, 148.0, 162.0, 164.7, 172.0. **18**: IR (film): 3506, 1782, 1750, 1722, 1639 cm^{-1}; δ_H ($CDCl_3$) 0.92 (3H, t, J= 7.4 Hz), 1.19 (3H, d, J= 6.4 Hz), 1.26 (3H, s), 1.33 (3H, s), 1.30 - 1.45 (2H, complex), 1.86 (1H, m), 2.01 (1H, m), 2.15 (1H, dd, J= 14, 7.2 Hz), 2.30 (1H, m), 3.37 (3H, s), 3.40 (1H, s), 3.57 (1H, s), 3.58 - 3.73 (3H, complex), 4.58 (1H, dd, J= 9.2, 1.6 Hz), 5.66 (1H, d, J= 15.6 Hz), 5.87 (1H, s), 6.06 (1H, d, J= 1.6 Hz), 6.09 - 6.19 (2H, complex), 7.13 (1H, m), 7.46 - 7.53 (3H, complex), 7.86 (2H, dd, J= 6.8, 1.6 Hz).